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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,092	05/18/1999	MICHAEL PAULISTA	P564-9010	9258

7590 10/23/2002

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	23

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,092	PAULISTA ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 08/07/02 has been acknowledged.

Claim 29 was canceled.
Claims 17, 20-21, 23, 26 and 28 were amended.
Claims 17-28 were pending and were examined in this office action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/07/02 has been entered.

Applicant's arguments filed 05/08/02 have been fully considered but they are not persuasive in view of new grounds of rejections below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

The instant claims are drawn to an implant for cartilage and/or bone growth comprising a crystallographically phase-pure calcium phosphate matrix and a cartilage and/or bone inducing MP52 protein or DNA encoding the MP52 protein, wherein the MP52 protein is selected from the group consisting of fragments of SEQ ID No:1, which is a homodimer (as claimed) and a dimer of another protein of TGF-beta super-family. The instant claims are further drawn to a method of treating a disease, which affect cartilage and/or bone and/or damage to cartilage and/or bone in a patient by implanting the implant material as claimed.

The specification states that many members of TGF-beta, BMP and GDF subfamilies have cartilage and/or bone inducing potentials. The specification further states that it can be assumed that a combination of various factors would be advantageous for the efficiency of cartilage and bone induction (spec. page 3, para.1). The specification further teaches the use of crystallographically phase-pure alpha and beta tricalcium phosphate ceramics in making of the implant as claimed (spec. 13, para.1). In addition the specification suggested that the efficacy of the implant material could be tested in conventional test systems such as animal models (spec. page 19-20).

However, the instant specification fails to disclose that the implantation of the implant material (as claimed) leads to bone or cartilage formation in any and all animals. The specification even fails to provide a single working example that a protein encoded by SEQ ID NO:1 or its fragments (as claimed) have any bone and/or cartilage inducing potential in any and all animals. The state of the art at the time of filing teaches that the signal transduction mechanism of members of TGF-beta superfamily is complex and the members are know to regulate plethora of developmental processes (Attisano et al, Science. 296:1646-1647, 20002). For example, proteins of the TGF-beta superfamily bind to two different types of signaling receptors termed as type II and type I receptors. Upon ligand binding and formation of type II and type I receptor complexes, followed by possible receptor conformational changes, type I receptors are phosphorylated and activated by type II receptor kinases. Type I receptor kinases

then transmit intracellular signals by phosphorylating Smad proteins. In mammals, only five type II receptors and seven type I receptors have been identified. It is theoretically possible to form more than 30 different combinations of type II and type I receptors. However, certain type II receptors tend to interact with certain type I receptors. Thus, the combinations of type II and type I receptors appear to be limited under physiological conditions and the variety of ligands converge at the receptor level (Miyazono et al, J Cell Physiol, 187(3):265-76, 2001). The instant specification fails to disclose that MP52 modulates bone and/or cartilage formation via TGF-beta signal transduction pathway. In addition, the specification fails to disclose what are another dimmer of TGF-beta superfamily that in combination with MP52 that would leads to cartilage and/or bone formation.

Furthermore, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The recited fragment of SEQ ID NO:1 are simply computer generated hypothesis since the specification fails to disclose that these fragments possess any bone or cartilage formation activity. In addition, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. Thus, in order to elucidate the roles of TGF-beta and a morphogenetic protein in clinical disorders it is very important to understand the signaling mechanisms of those proteins in vivo (see Miyazono, page 272, conclusion).

Besides protein therapy the scope of invention as claimed encompasses a method for gene therapy. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25

col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case considering the complexities of the members TGF-beta superfamily the specification as filed fails provide a single working example that establishes that SEQ ID NO:1 or its fragments (as claimed) has any bone and/or cartilage inducing potential in-vivo.

In addition the invention as claimed requires the transduction of target cells via a DNA molecule encoding the MP52 protein. The state of the art at the time of filing was such that it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and

therefore would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4).

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case MP52 protein and gene based therapies are not routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Thus, in view of lack of specific guidance in the specification, the skilled artisan at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making an implant as claimed, containing fragments of MP52 protein (as claimed) in combination with any and all dimmer of TGF-beta superfamily and testing the implant for bone and/or cartilage inducing activity in vivo for the treatment of any bone defect, sinus lift, cyst filling cosmetic application, plastic surgery in dental region and periodontosis.

Claim Objections

Claims 25-28 are objected to because of the following informalities: Claims 25 and 28 recite limitation "and/or" in plurality. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem Yucel Ph.D. can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
Patent examiner

Scott D. Priebe
SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER